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| EXAMINER |
|---|
| BOWERS, NATHAN ANDREW |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/688,905 | KIRK ET AL. | |
| | Examiner | Art Unit | |
| | Nathan A. Bowers | 1744 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *031907*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kricka (US 5744366) in view of Dubrow (US 6251343).

With respect to claim 1, Kricka discloses a method of monitoring chemotaxis comprising providing a housing (Figure 10:10) defining a plurality of chambers. Each chamber includes a first well (Figure 10:22a), a second well (Figure 10:32), and a channel region connecting the first well and the second well with one another. This is described in column 6, lines 4-14, column 11, lines 5-36 and column 15, lines 45-53. Column 8, lines 8-20 and column 14, lines 18-31 state that a soluble test substance is introduced in the first well of each the chambers, and that a concentration gradient is formed along a longitudinal axis of the plurality of chambers. Cells are introduced into each of the second wells, and chemotaxis of the cells is monitored. Additionally, Kricka teaches that the housing comprises a support member (Figure 1:14) and a top member (Figure 1:12) mounted to the support member by being placed in substantially fluid-tight conformal contact with the support member. This is suggested by the cross-sectional representation presented in Figure 1. Kricka describes the arrangement as being fluid-tight numerous times throughout the disclosure. Kricka, however, does not expressly disclose that the top member of the housing is removably sealed to the support member.

Dubrow discloses a microfluidic device that comprises a top member (Figure 1:102) mounted to a support member (Figure 1:110). Flow channels (Figure 1:114) are provided to deliver analytes to a target region (Figure 1:116) where any subsequent reaction is monitored. The top member and support member are in form-fitting, conformal contact. This is apparent from Figure 1. Column 8, line 66 to column 9, line 12 indicates that the cover is fabricated from PDMS. Column 9, lines 25-38 state that the top member and support member are removably sealed using a clamping system.

Kricka and Dubrow are analogous art because they are from the same field of endeavor regarding microfluidic analysis devices.

At the time of the invention, it would also have been obvious to attach the top member and support members disclosed by Kricka in such a way that they are in conformal contact with one another. As evidenced by Dubrow, these types of fluid-tight seals are well known in the art. By ensuring that the top and support members are pressed together in "substantially fluid-tight, form-fitting contact," one would be able to reduce the likelihood of contamination and the formation of leaks during use. Creating a conformal fitting between the top and support members would not render Kricka's device inoperable, and would require only minor structural changes.

With respect to claims 9 and 10, Kricka and Dubrow disclose the method in claim 1 wherein introducing cells in the second well comprises placing either a single cell type or a mixture of cell types in the channel. Column 14, lines 18-31 of Kricka describe one embodiment in which only one selected cell type is deposited in the channel. Column 4, lines 59-63 state that is known to place a mixture of cell types in the channel.

2) Claims 1, 2, 9-11, 17, 18, 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarnagin (US 6238874) in view of Dubrow (US 6251343).

With respect to claim 1, Jarnagin discloses a method for monitoring chemotaxis comprising providing a housing defining a plurality of chambers (Figure 5:98). Each chamber includes a first well region (Figure 5:92) connected to a second well region (Figure 5:80, 82, 84,

86, 88, 90) via a channel region (Figure 5:94). This is described in column 7, lines 6-46 and column 10, line 41 to column 11, line 33. Jarnagin teaches that a soluble test substance is introduced to each of the first wells in order to produce a concentration gradient along a longitudinal axis of the plurality of chambers. Cells are introduced into the second well, and subsequent chemotactic behavior is monitored. Jarnagin, however, does not expressly indicate that a top member of the housing is removably sealed to a support member with substantially tight, conformal contact.

Dubrow discloses a microfluidic device that comprises a top member (Figure 1:102) mounted to a support member (Figure 1:110). Flow channels (Figure 1:114) are provided to deliver analytes to a target region (Figure 1:116) where any subsequent reaction is monitored. The top member and support member are in form-fitting, conformal contact. This is apparent from Figure 1. Column 8, line 66 to column 9, line 12 indicates that the cover is fabricated from PDMS. Column 9, lines 25-38 state that the top member and support member are removably sealed using a clamping system.

Jarnagin and Dubrow are analogous art because they are from the same field of endeavor regarding microfluidic analysis devices.

At the time of the invention, it would also have been obvious to attach the top member and support members disclosed by Jarnagin in such a way that they are in conformal contact with one another. As evidenced by Dubrow, these types of fluid-tight seals are well known in the art. By ensuring that the top and support members are pressed together in "substantially fluid-tight, form-fitting contact," one would be able to reduce the likelihood of contamination and the formation of leaks during use. Creating a conformal fitting between the top and support

members would not render Jarnagin's device inoperable, and would require only minor structural changes.

With respect to claim 2, Jarnagin and Dubrow disclose the method in claim 1 wherein the channels contain a gel matrix. This is taught by Jarnagin in column 11, lines 5-15.

With respect to claims 9 and 10, Jarnagin and Dubrow disclose the method in claim 1 wherein the second well is supplied with a sample solution containing either a single cell type or a mixture of cell types. Jarnagin discloses the use of mixed cell samples in column 2, lines 65-67 and throughout the reference. In column 11, lines 24-33, Jarnagin states that individual cell types are handled separately and simultaneously.

With respect to claim 11, Jarnagin and Dubrow disclose the method in claim 1. Additionally, Jarnagin states that a plurality of channels (Figure 5:94) are used to connect the first and second well regions. In column 11, lines 24-33, Jarnagin indicates that different cell types are positioned in each of the plurality of channels.

With respect to claims 17 and 18, Jarnagin and Dubrow disclose the method in claim 1 wherein a plurality of channels are disposed between the first and second well regions. In column 15, lines 32-48, Jarnagin states that either individual cell types or a mixture of cell types are introduced into each of the plurality of channels.

With respect to claims 22 and 24, Jarnagin and Dubrow disclose the method in claim 1 wherein a plurality of channels are disposed between the first and second well regions. A single test substance is deposited in the first well and moves into the plurality of channels, thereby forming a plurality of the test substances that are identical. This is apparent from Figures 4 and 5, and from columns 9-11 of Jarnagin.

3) Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Kricka (US 5744366) or Jarnagin (US 6238874) each in view of Dubrow (US 6251343) as applied to claim 1, and further in view of Goodwin Jr. (US 5284753).

The combinations of Kricka with Dubrow and Jarnagin with Dubrow each disclose the method set forth in claim 1 as set forth in the 35 U.S.C. 103 rejections above. Kricka and Jarnagin each indicate that the plurality of chambers are used to simultaneously test a plurality of substances in order to determine their effects on cell migration. In column 5, line 63 to column 6, line 14 and column 14, line 18-32, Kricka teaches that it is known to introduce different and identical test substances into the plurality of chambers. Kricka and Jarnagin, however, are silent with regard to the relative concentrations of the substances in each chamber.

Goodwin Jr. discloses a membrane (Figure 2:11) through which migrating cells are allowed to pass through in response to a chemotactic agent. Cells are monitored as they move from a cell suspension (Figure 2:16) to a fluid area (Figure 2:17) that contains a chemoattractant. Goodwin Jr. describes the use of a plurality of chambers that accommodate fluid areas at varying concentrations. This is disclosed in column 4, line 24 to column 5, line 7.

Kricka, Jarnagin and Goodwin Jr. are analogous art because they are from the same field of endeavor regarding chemotaxis methods.

At the time of the invention, it would have been obvious to introduce a plurality of chemotactic substances into the plurality of chambers individually disclosed by Kricka and Jarnagin in such a way that the concentrations of the chemotactic substances are different. This would have been beneficial because it would have allowed one to monitor cell response based on the relative strength of a substance. In this way, one would be able to determine which substance induces the most desirable chemotactic cellular response, but whether or not this response is dependent on the amount of the substance added to the chamber. Analyzing the affects of concentration, as well as substance composition, leads to a more sophisticated and thorough analysis.

4) Claims 3-5, 12, 13 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarnagin (US 6238874) in view of Dubrow (US 6251343) as applied to claims 1 and 11, and further in view of Kennedy "Motility and chemotaxis in *Serpulina hyodysenteriae*" and/or Shonnard "Hydrodynamic effects on microcapillary motility..."

Jarnagin and Dubrow disclose the methods set forth in claims 1 and 11 as set forth in the 35 U.S.C. 103 rejection above. Jarnagin teaches that it is known to provide a housing comprising a plurality of chambers, wherein each chamber includes a first well region, a second well region, and a plurality of channels that connect the first and second well regions. Different cell types are introduced in each of the plurality of channels. Jarnagin, however, does not disclose that the cells are provided at different concentrations. Jarnagin does not expressly

indicate that different test substances are introduced into each of the channels at different concentrations.

Kennedy and Shonnard each describe experiments in which chemotaxis conditions are optimized. Samples comprising different concentrations of cells are allowed to interact with different test substances supplied at a variety of concentrations. This is described throughout the Kennedy reference, especially in Figure 1 and Table 1. Shonnard teaches this in the "Optimal conditions for chemotaxis" section.

Jarnagin, Kennedy and Shonnard are analogous art because they are from the same field of endeavor regarding chemotaxis systems.

At the time of the invention, it would have been obvious to ensure that Jarnagin's method is used to simultaneously test a plurality of different cell types supplied at different concentrations with a plurality of test substances supplied at a variety of concentrations. This arrangement would have been desirable because it would have allowed one the ability to more thoroughly characterize conditions in which cell chemotaxis is optimum. Furthermore, it would have allowed one to study the hydrodynamic effects on cell motility that arise when high concentrations of test substances are introduced to the channel system (See Shonnard). It is believed that methods that utilize same or different cell types at same or different concentrations are known in the chemotaxis art, as well as methods that utilize same or different test substances supplied at same or different concentrations.

5) Claims 3 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Jarnagin (US 6238874) or Kricka (US 5744366) each in view of Dubrow (US 6251343) as applied to claim 1, and further in view of Jeon (US 6705357)

The combinations of Jarnagin with Dubrow and Kricka with Dubrow each disclose the method set forth in claim 1 as set forth in the 35 U.S.C. 103 rejections above, however do not expressly disclose that first and second substances are introduced by first and second streams that produce a concentration gradient that is perpendicular to the direction of flow. Jarnagin and Kricka do not disclose the use of laminar flow.

Jeon discloses an apparatus for combining and splitting different fluids in order to produce concentration gradients. First and second fluid streams converge into a single third fluid stream characterized by a concentration gradient that is substantially perpendicular to the direction of fluid flow. The third stream diverges into separate fourth, fifth, and sixth streams, and then re-converges into a single seventh stream. Jeon teaches that concentration gradients are formed under laminar flow. This is described in Figure 14, and in column 2, lines 7-33, column 4, line 25 to column 5, line 21, column 12, lines 5-23, and column 13, lines 41-51.

Jarnagin, Kricka and Jeon are analogous art because they are from the same field of endeavor regarding chemotaxis systems.

At the time of the invention, it would have been obvious to modify the methods described by Jarnagin and Kricka in order to create a system in which streams carrying test substances are combined into a common stream, split into a new set of separate streams, and then re-combined to produce a concentration gradient that is perpendicular to the direction of fluid flow. Jeon teaches in column 4, line 66 to column 5, line 21 that this is an effective way to create gradients

for the study of chemotactic cells. Jeon further indicates that splitting and combining streams under laminar flow conditions results in a device capable of attaining a steady state in which chemical concentrations at any position in the gradient are stable.

6) Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarnagin (US 6238874) in view of Dubrow (US 6251343) as applied to claim 1, and further in view of Kricka (US 5744366).

Jarnagin and Dubrow disclose the method set forth in claim 1 as set forth in the 35 U.S.C. 103 rejection above. Jarnagin teaches that it is known to provide a housing comprising a plurality of chambers, wherein each chamber includes a first well region, a second well region, and a plurality of channels that connect the first and second well regions. Jarnagin, however, does not expressly disclose that a single cell type is provided in each of the plurality of channels.

Kricka discloses the method as previously described above. In column 5, line 63 to column 6, line 14, Kricka states that it is known in the art to use multi-channel devices to generate replicate sets of data by conducting a plurality of identical flow systems.

At the time of the invention, it would have been obvious to introduce a single cell type in each of the plurality of channels disclosed by Jarnagin. This would have been beneficial because it would have allowed one to easily and simultaneously generate replicate sets of data each representing the same experimental conditions. It would have also been obvious to introduce a single cell type in each of the plurality of channels at varied concentrations in order to measure the effect of cell concentration on migration. With all other variables held constant, this would

have been an effective way to selectively measure how cell concentration, not cell type, influences the rate of chemotaxis.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7) Claims 1, 2 and 25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 11 of U.S. Patent No. 6811968. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant invention are generic to the claims of U.S. Patent No. 6811968. U.S. Patent No. 6811968 specifically discloses a method of chemotaxis that includes the use of first and second wells and a channel for forming a solution concentration gradient.

8) Claims 1 and 25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5-7 and 11 of U.S. Patent No. 6818403. Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art would understand that the method of haptotaxis disclosed in U.S. Patent No. 6818403 could easily be amended to produce a method of chemotaxis. U.S. Patent No. 6818403 specifically discloses the use of first and second wells and a channel for forming a solution concentration gradient.

9) Claims 1, 2 and 25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 17 and 18 of U.S. Patent No. 6982171. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant invention are generic to the claims of U.S. Patent No. 6982171. U.S. Patent No. discloses a method of chemotaxis drawn to the use of specific cell types and substances. U.S. Patent No. discloses the use of first and second wells and a channel for forming a solution concentration gradient.

***Response to Arguments***

Applicant's arguments filed 19 March 2007 with respect to the 35 U.S.C. 102 rejections involving Kricka and Jarnagin have been fully considered and are persuasive. Therefore, these rejections have been withdrawn. However, upon further consideration, a new ground of rejection is made in view of the combination of Kricka with Dubrow and the combination of Jarnagin with Dubrow.

Dubrow addresses the deficiencies of Kricka and Jarnagin by indicating that it is known in the art to provide a removable cover for sealing a microfluidic system. By ensuring that the top and support members are pressed together in "substantially fluid-tight, form-fitting contact," one would be able to reduce the likelihood of contamination and the formation of leaks during use.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan A. Bowers whose telephone number is (571) 272-8613. The examiner can normally be reached on Monday-Friday 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gladys Corcoran can be reached on (571) 272-1214. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NAB

GLADYS JP CORCORAN
SUPERVISORY PATENT EXAMINER